REMARKS

Claims 51-60 have been cancelled. Claims 43 and 65 have been amended. New claims 67-69 are added. Claims 43-50 and 61-69 are now pending in this application. Claim 65 has been amended to correct a typographical error. Support for the remaining amendments is found in the existing claims and the specification as discussed below. Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

Personal Interview

Applicants' representative would like to thank Examiner Helms for the productive interview on June 25, 2003 with Nico Mertens, Philippe Jacobs, Johan Brants, Ann DeClercq, Daniel Altman and Che Chereskin. During the interview, claim amendments were discussed to more clearly differentiate Applicants' claimed invention from the cited references.

Allowable Subject Matter

Applicants gratefully acknowledge the Examiner's indication of allowable subject matter for claims 45 and 50. Claims 45 and 50 have been rewritten in independent form as claims 68 and 69.

Rejections under 35 U.S.C. § 103(a)

Claims 43-44, 46-49, 61-62, and 64-66 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Carter and further in view of Chester et al.

In response to arguments presented previously, the Examiner asserts that Carter teaches that the hinge region can be entirely omitted in favor of a single cysteine or a cysteine containing peptide. The Examiner also cites Paul, et al. to provide a definition of "hinge" region which states that a hinge region contains numerous residues in addition to cysteines. The Examiner concludes that a single cysteine is not therefore a hinge region.

In response, Applicants have amended claim 43 to more clearly set forth the invention. The negative limitation regarding the hinge region has been deleted and, as discussed during the interview of June 25th, the claims now specify that linkage between the CL, VL, CH1 and VH domains and the molecule having at least one further purpose is accomplished via a peptide

bond. New claim 67 also adds this limitation. Support for this amendment is found, for example, at page 5, lines 10-11; and page 8, lines 6-11 of the specification and in the figures. Figures 3A and 3B show peptide linkers according to the invention. Furthermore, note that these linkers do not include a cysteine (see Figures 3A and 3B and specification at page 16, line 36, for example).

In contrast, Carter teaches either a hinge region or at least a single cysteine or a short peptide containing a single cysteine (col. 8, lines 19-23). Linkage occurs via a sulfhydryl bond to a cysteine from the hinge regions of the CH1 domain or any other sequence containing a single free thiol cysteinyl residue (see col. 5, lines 7-17). Thus, Applicants' invention differs from Carter in that Applicants teach linkage through a peptide bond, rather than a sulfhydryl bond.

Applicants' invention has the advantage that the peptide bond is stronger and more stable than a disulfide bond. The disulfide bond is not stable under reducing conditions. Applicants' invention has the further advantage in that formation of unwanted homodimers via the free sulfhydryl groups is avoided because the recombinant antibodies of Applicants do not contain a hinge region and do not contain free thiols.

The Examiner also asserts that Chester teaches molecules fused to the CL and Carter, et al. teaches additions to C-terminus or N-terminus of the Fabs so that it would have been obvious to couple other molecules to the C terminus of the CL and the CH1.

In response, neither reference teaches coupling two or more molecules to two or more of the antibody domains. For example, Carter teaches that "**either** of the Fv light **or** heavy chains optionally is fused to an immunoglobulin sequence which contains one or more cysteinyl residues, provided that at least one of such cysteinyl residues in the domain C-terminal to **either** the light **or** heavy chain Fv is present as the free thiol in the periplasm" (col. 4, line 66 to col. 5, line 4, emphasis added). Thus, Carter clearly teaches fusion to either the heavy or the light chain, not both. Chester, et al. does not correct the deficiencies of Carter as Chester, et al. diagrammatically shows only one toxin or enzyme molecule fused to the CL. Consequently, there is no motivation in either of Chester, et al. or Carter to fuse two or more molecules to two or more domains.

Furthermore, it was unexpected that one could attach two or more molecules to two or more domains and still allow interaction of the CH1-VH and the CL-VL because of potential steric hindrance and electrostatic repulsion between the attached molecules.

In conclusion, the cited references neither teach nor suggest coupling of two or more molecules to two or more domains by a peptide bond as discussed above. In view of Applicants' amendments and arguments, reconsideration and withdrawal of this ground of rejection is respectfully requested.

Claims 43-44, 46-49, and 61-66 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Carter and further in view of Tutt, et al.

The Examiner maintains that Tutt, et al. teach trispecific antibodies which are used to target and that it would be obvious to produce trispecific Fabs in view of Tutt, et al. combined with the teaching of Carter on Fab-SH molecules and Fabs with peptide linkers which contain a cysteine residue.

Carter has been discussed above which discussion is incorporated here by reference. For the reasons given above, the present claims are believed to be patentable over Carter.

Tutt, et al. do not correct the deficiencies of Carter as Tutt, et al. is drawn to a chemical coupling using the hinge region. Also, even though the molecule shown in Figure 1 of Tutt, et al. is trispecific, there is still only one function per Fab' fragment. In contrast, Applicants' claimed invention is directed towards an entirely different concept, i.e., having two or more additional molecules linked to a single Fab fragment (without hinge region).

It is respectfully submitted that all claims are now patentable over the cited references. It is respectfully requested that the Examiner reconsider and withdraw all grounds of rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: July 9, 2003

By: Che S. Chereskin
Che Swyden Chereskin
Registration No. 41,466
Agent of Record
Customer No. 20,995

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